FILE 'USPAT' ENTERED AT 09:45:35 ON 09 SEP 1997

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  *                                                             *
  *              W E L C O M E   T O   T H E                    *
  *         U. S.   P A T E N T   T E X T   F I L E             *
  *                                                             *
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=> s vascular endothelial growth factor
         15734 VASCULAR
          4014 ENDOTHELIAL
        125665 GROWTH
        231766 FACTOR
L1          67 VASCULAR ENDOTHELIAL GROWTH FACTOR
               (VASCULAR(W)ENDOTHELIAL(W)GROWTH(W)FACTOR)

=> s vegf3
L2           0 VEGF3

=> s vegf
L3          42 VEGF

=> s l1 or l3
L4          72 L1 OR L3

=> d 1-20
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1. 5,663,304, Sep. 2, 1997, Refolding of misfolded insulin-like growth factor-I; Stuart Builder, et al., 530/399; 435/69.4, 172.3, 252.3, 320.1; 530/418, 420, 422, 424

2. 5,663,064, Sep. 2, 1997, Ribozymes with RNA protein binding site; John M. Burke, et al., 435/172.3, 6, 91.31, 172.1, 320.1, 325, 410; 514/44; 536/23.1, 23.2, 24.5 :IMAGE AVAILABLE:

3. 5,661,135, Aug. 26, 1997, Human **VEGF**-specific oligonucleotides; Gregory S. Robinson, 514/44; 435/6; 536/23.5, 24.3, 24.31, 24.33, 24.5 :IMAGE AVAILABLE:

4. 5,660,827, Aug. 26, 1997, Antibodies that bind to endoglin; Philip E. Thorpe, et al., 424/152.1, 130.1, 138.1, 141.1; 530/387.1, 388.1 :IMAGE AVAILABLE:

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6. 5,654,404, Aug. 5, 1997, Protection against liver damage by HGF; Filip Roos, et al., 530/387.3; 424/134.1, 136.1, 178.1; 530/350 :IMAGE AVAILABLE:

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343.2; 530/387.1, 388.24, 391.3 :IMAGE AVAILABLE:

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14. 5,650,275, Jul. 22, 1997, Target detection method using spectroscopically detectable nucleic acid ligands; J. Bruce Pitner, et al., 435/6; 935/77, 78 :IMAGE AVAILABLE:

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16. 5,641,783, Jun. 24, 1997, Substituted amino alcohol compounds; J. Peter Klein, et al., 514/263, 183, 222.5, 223.5, 224.2, 226.8, 227.5, 228.8, 229.2, 230.5, 230.8, 237.8, 241, 242, 243, 246, 247, 248, 249, 255, 256, 258, 259, 261, 262, 270, 274, 297, 300, 301, 302, 303, 306, 307, 311, 312, 315, 345, 351, 357, 359, 360, 361, 362, 363, 364, 365, 367, 369, 372, 373, 374, 375, 376, 378, 379, 380, 381, 383, 389, 394, 395, 398, 399, 401, 404, 406, 413, 415, 416, 418, 423, 424, 425, 427, 428; 544/1, 2, 3, 8, 53, 63, 65, 66, 67, 90, 91, 162, 215, 216, 219, 220, 224, 235, 239, 254, 255, 257, 262, 272 :IMAGE AVAILABLE:

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20. 5,639,872, Jun. 17, 1997, Human **VEGF**-specific oligonucleotides; Gregory S. Robinson, 536/24.5; 435/6; 536/23.5, 24.3, 24.31, 24.33 :IMAGE AVAILABLE:

=> d 6 fro

US PAT NO: 5,654,404 :IMAGE AVAILABLE: L4: 6 of 72
DATE ISSUED: Aug. 5, 1997
TITLE: Protection against liver damage by HGF
INVENTOR: Filip Roos, Brisbane, CA
Ralph Schwall, Pacifica, CA
ASSIGNEE: Genentech, Inc., So. San Francisco, CA (U.S. corp.)
APPL-NO: 08/419,654
DATE FILED: Apr. 10, 1995
REL-US-DATA: Division of Ser. No. 310,361, Sep. 21, 1994, which is a continuation of Ser. No. 968,711, Oct. 30, 1992, abandoned, which is a continuation-in-part of Ser. No. 946,263, Sep. 16, 1992, abandoned.

INT-CL: :6: C07K 14/435; C12P 21/08; A61K 39/00; A61K 38/16
US-CL-ISSUED: 530/38[redacted], 350; 424/134.1, 136.1, 178.1[redacted]
US-CL-CURRENT: 530/387.3; 424/134.1, 136.1, 178.1; 530/[redacted]50
SEARCH-FLD: 530/389.2, 387.3, 399, 350; 424/138.1, 124.1, 145.1; 514/12, 2

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ART-UNIT: 186
PRIM-EXMR: Lila Feisee
ASST-EXMR: John Lucas
LEGAL-REP: Merchant, Gould, Smith, Edell, Welter & Schmidt

ABSTRACT:
The present invention provides methods for preventing occurrence or progression of liver damage using hepatocyte growth factor. In the methods, a preventatively effective amount of the hepatocyte growth factor is administered to the patient. The hepatocyte growth factor can be administered, for instance, prior to administering a hepatotoxic therapy to the patient. The hepatocyte growth factor can further be administered with activin or transforming growth factor-beta to prevent liver damage. Compositions comprising hepatocyte growth factor and activin antagonist or transforming growth factor-beta antagonist are also provided by the invention.
18 Claims, 9 Drawing Figures

=> d 21-40

21. 5,639,868, Jun. 17, 1997, High-affinity RNA ligands for basic fibroblast growth factor; Nebojsa Janjic, et al., 536/22.1; 435/6, 91.2; 935/77, 78 :IMAGE AVAILABLE:

22. 5,639,736, Jun. 17, 1997, Human **VEGF**-specific oligonucleotides; Gregory S. Robinson, 514/44; 435/6, 375; 536/24.5 :IMAGE AVAILABLE:

23. 5,639,725, Jun. 17, 1997, Angiostatin protein; Michael S. O'Reilly, et al., 514/12; 424/94.64; 435/69.1, 217; 530/350, 380 :IMAGE AVAILABLE:

24. 5,639,635, Jun. 17, 1997, Process for bacterial production of polypeptides; John C. Joly, et al., 435/69.1; 536/23.5, 23.6, 23.7 :IMAGE AVAILABLE:

25. 5,635,388, Jun. 3, 1997, Agonist antibodies against the flk2/flt3 receptor and uses thereof; Brian D. Bennett, et al., 435/334; 424/85.1, 85.2, 85.5; 435/70.21, 172.2, 320.1, 328; 530/351, 387.3, 388.22, 389.1; 536/23.53 :IMAGE AVAILABLE:

26. 5,633,165, May 27, 1997, Fermentor with vertical shaft; James R. Swartz, 435/287.1, 286.7, 287.5, 289.1 :IMAGE AVAILABLE:

27. 5,626,561, May 6, 1997, Implantable containment apparatus for a therapeutical device and method for loading and reloading the device therein; Mark D. Butler, et al., 604/49, 93, 890.1 :IMAGE AVAILABLE:

28. 5,614,642, Mar. 25, 1997, Methods of inhibiting phosphatase activity

and treatment of disorders associated therewith using naphthopyrones and derivatives thereof; Peng C. Tang, et al., 549/389 :IMAGE AVAILABLE:

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30. 5,607,918, Mar. 4, 1997, **Vascular endothelial growth factor**-B and DNA coding therefor; Ulf Eriksson, et al., 514/12; 530/350 :IMAGE AVAILABLE:

31. 5,605,791, Feb. 25, 1997, Carbohydrate-directed cross-linking reagents; Avi J. Ashkenazi, et al., 435/5, 7.1; 548/546 :IMAGE AVAILABLE:

32. 5,602,301, Feb. 11, 1997, Non-human mammal having a graft and methods of delivering protein to myocardial tissue; Loren J. Field, 800/2; 424/93.21, 93.7; 435/69.1; 800/DIG.5; 935/60, 62 :IMAGE AVAILABLE:

33. 5,602,171, Feb. 11, 1997, Methods of inhibiting phosphatase activity and treatment of disorders associated therewith using naphthopyrones and derivatives thereof; Peng C. Tang, et al., 514/455; 549/389 :IMAGE AVAILABLE:

34. 5,580,979, Dec. 3, 1996, Phosphotyrosine peptidomimetics for inhibiting SH2 domain interactions; William W. Bachovchin, 540/509, 505, 510, 511, 542, 569, 570, 571, 572 :IMAGE AVAILABLE:

35. 5,580,722, Dec. 3, 1996, Methods of determining chemicals that modulate transcriptionally expression of genes associated with cardiovascular disease; J. Gordon Foulkes, et al., 435/6, 91.1, 91.2; 935/77, 78 :IMAGE AVAILABLE:

36. 5,580,569, Dec. 3, 1996, Article for tissue-specific delivery of therapeutic agents; Vincent C. Giampapa, 424/426; 514/772.6, 774, 953; 604/57; 606/46 :IMAGE AVAILABLE:

37. 5,569,602, Oct. 29, 1996, First immortalized Kaposi's sarcoma cell line; Yanto Lunardi-Iskandar, et al., 435/366, 379 :IMAGE AVAILABLE:

38. 5,561,053, Oct. 1, 1996, Method for selecting high-expressing host cells; Craig W. Crowley, 435/69.1, 172.3, 320.1, 358; 536/23.2 :IMAGE AVAILABLE:

39. 5,549,674, Aug. 27, 1996, Methods and compositions of a bioartificial kidney suitable for use in vivo or ex vivo; H. David Humes, et al., 623/11; 514/12; 600/36; 604/6, 35, 48, 319; 623/1, 12 :IMAGE AVAILABLE:

40. 5,506,107, Apr. 9, 1996, Selecting ligand agonists and antagonists; Brian C. Cunningham, et al., 435/7.21, 7.8; 436/501, 537 :IMAGE AVAILABLE:

=> d 30 clms

US PAT NO: 5,607,918 :IMAGE AVAILABLE: L4: 30 of 72

CLAIMS:

CLMS(1)

What is claimed is:

1. An isolated protein having the property of promoting proliferation of endothelial cells or mesodermal cells, said isolated protein comprising a sequence of amino acids selected from the group consisting of the amino

acid sequence of FIG. [redacted] (SEQ ID NO:2), the amino acid sequence of FIG. 2 (SEQ ID NO:3), the am acid sequence of FIG. 4 (SEQ [redacted]NO:5), the amino acid sequence of FIG. 6 (SEQ ID NO:7), the amino acid sequence of FIG. 8 (SEQ ID NO:9), and the amino acid sequence of FIG. 11 (SEQ ID NO:11).

CLMS(2)

2. An isolated protein according to claim 1, wherein said protein comprises the amino acid sequence of FIG. 1 (SEQ ID NO:2).

CLMS(3)

3. An isolated protein according to claim 1, wherein said isolated protein comprises the amino acid sequence of FIG. 2 (SEQ ID NO:3).

CLMS(4)

4. An isolated protein according to claim 1, wherein said isolated protein comprises the amino acid sequence of FIG. 4 (SEQ ID NO:5).

CLMS(5)

5. An isolated protein according to claim 1, wherein said isolated protein comprises the amino acid sequence of FIG. 6 (SEQ ID NO:7).

CLMS(6)

6. An isolated protein according to claim 1, wherein said isolated protein comprises the amino acid sequence of FIG. 8 (SEQ ID NO:9).

CLMS(7)

7. An isolated protein according to claim 1, wherein said isolated protein comprises the amino acid sequence of FIG. 11 (SEQ ID NO:11).

CLMS(8)

8. An isolated protein according to claim 1, wherein said isolated protein is a mammalian protein.

CLMS(9)

9. An isolated protein according to claim 8, wherein said mammalian protein is a murine protein.

CLMS(10)

10. An isolated protein according to claim 8, wherein said mammalian protein is a human protein.

CLMS(11)

11. An isolated protein according to claim 1, wherein said isolated protein promotes proliferation of vascular endothelial cells.

CLMS(12)

12. An isolated protein produced by expression of a DNA selected from the group consisting of the DNA of FIGS. 1 and 2 (SEQ ID NO:1), the DNA of FIG. 3 (SEQ ID NO:4), the DNA of FIG. 5 (SEQ ID NO:6), the DNA of FIG. 7 (SEQ ID NO:8), the DNA of FIG. 10 (SEQ ID NO:10), and DNA which hybridizes under stringent conditions with at least one of the foregoing DNA sequences.

CLMS(13)

13. A pharmaceutical composition comprising an effective endothelial or mesodermal cell proliferation promoting amount of an isolated protein according to claim 1, and at least one pharmaceutical carrier or diluent.

=> d 41-60

41. 5,494,677, Feb. 27, 1996, Tissue-specific implantable therapeutic agent delivery system; Vincent C. Giampapa, 424/426; 514/772.6, 774 :IMAGE AVAILABLE:

42. 5,487,980, Jan. 30, 1996, Method of determining propensity of dissolved oxygen instability; James R. Swartz, 435/29, 69.1 :IMAGE AVAILABLE:

43. 5,486,599, Jan. 23, 1996, Construction and use of synthetic constructs encoding syndecan; Scott Saunders, et al., 530/395; 435/69.1, 69.7, 252.3, 320.1; 536/23.4, 23.5; 935/10, 47, 50, 70 :IMAGE AVAILABLE:

44. 5,480,975, Jan. 2, 1996, Induction of **vascular endothelial growth factor** (**VEGF**) by transition metals; Mark A. Goldberg, et al., 530/399; 424/484, 617, 630, 639, 641, 642, 646, 655 :IMAGE AVAILABLE:

45. 5,470,878, Nov. 28, 1995, Cell signaling inhibitors; John Michnick, et al., 514/558, 258, 262, 274, 299, 315, 418, 425, 529, 552, 561, 613, 617, 626, 629, 669; 544/254, 285, 301; 546/183, 243; 548/486, 556 :IMAGE AVAILABLE:

46. 5,464,815, Nov. 7, 1995, Inhibition of heparin-binding; Steven Chamow, et al., 514/8; 424/85.2; 436/86, 87; 514/21; 530/412 :IMAGE AVAILABLE:

47. 5,459,015, Oct. 17, 1995, High-affinity RNA ligands of basic fibroblast growth factor; Nebojsa Janjic, et al., 435/6, 91.2; 935/77, 78 :IMAGE AVAILABLE:

48. 5,451,660, Sep. 19, 1995, Method for purifying polypeptides; Stuart E. Builder, et al., 530/344, 300, 324, 350, 351, 399, 413 :IMAGE AVAILABLE:

49. 5,444,151, Aug. 22, 1995, Platelet derived growth factor antagonists; Flemming S. Vassbotn, et al., 530/324, 325, 326, 327, 350, 399, 402, 408; 930/120 :IMAGE AVAILABLE:

50. 5,443,508, Aug. 22, 1995, Subcutaneous implantable multiple agent delivery system; Vincent C. Giampapa, 623/11; 424/424, 425; 604/891.1 :IMAGE AVAILABLE:

51. 5,407,810, Apr. 18, 1995, Aqueous multiple-phase isolation of polypeptide; Stuart Builder, et al., 435/69.1, 804; 530/399, 412, 422, 808 :IMAGE AVAILABLE:

52. 5,391,164, Feb. 21, 1995, Subcutaneous implantable multiple-agent delivery system; Vincent C. Giampapa, 604/891.1; 424/424, 425 :IMAGE AVAILABLE:

53. 5,384,331, Jan. 24, 1995, Ketamine analogues for treatment of thrombocytopenia; Timothy P. Kogan, et al., 514/646, 647, 648; 548/304.1; 558/262; 564/192, 194, 219, 221; 568/329 :IMAGE AVAILABLE:

54. 5,382,514, Jan. 17, 1995, In vivo angiogenesis assay; Antonino Passaniti, et al., 435/7.21; 424/520, 572; 435/7.23, 29; 436/63, 64, 813 :IMAGE AVAILABLE:

55. 5,342,763, Aug. 30, 1994, Method for producing polypeptide via bacterial fermentation; James R. Swartz, 435/69.1, 71.1; 530/401 :IMAGE AVAILABLE:

56. 5,336,518, Aug. 9, 1994, Treatment of metallic surfaces using radiofrequency plasma deposition and chemical attachment of bioactive agents; Pallassana V. Narayanan, et al., 623/1; 424/422, 423; 427/2.25, 470; 530/815, 816 :IMAGE AVAILABLE:

57. 5,332,671, Jul. 26, 1994, Production of vascular endothelial cell growth factor and DNA encoding same; Napoleone Ferrara, et al., 435/360, 69.4, 69.6, 320.1; 536/23.5, 23.51 :IMAGE AVAILABLE:

58. 5,329,028, Jul. 12, 1994, Carbohydrate-directed cross-linking reagents; Avi J. Ashkenazi, et al., 548/548, 546, 547, 549 :IMAGE AVAILABLE:

59. 5,326,695, Jul. 5, 1994, Platelet derived growth factor agonists; Maria Andersson, et al., 435/70.1, 243, 244, 320.1, 365; 530/350, 399; 536/23.5, 23.51 :IMAGE AVAILABLE:

60. 5,326,568, Jul. 5, 1994, Method of tissue-specific delivery; Vincent C. Giampapa, 424/426, 423, 424; 604/890.1, 892.1; 623/11 :IMAGE AVAILABLE:

```
FILE 'HOME' ENTERED AT 09:55:03 ON 09 SEP 1997

=> s vascular endothelial growth factor or vegf

THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Some commands only work in certain files.  For example, the EXPAND
command can only be used to look at the index in a file which has an
index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
commands which can be used in this file.

=> file medline

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.15       0.15

FILE 'MEDLINE' ENTERED AT 09:55:28 ON 09 SEP 1997

 FILE LAST UPDATED: 8 SEP 1997 (19970908/UP).  FILE COVERS 1966 TO DATE.
 +QLF/CT SHOWS YOU THE ALLOWABLE QUALIFIERS OF A TERM.

 MEDLINE ANNUAL RELOAD AVAILABLE ON STN IN RECORD TIME (2/08/97).
 ENTER HELP RLOAD FOR DETAILS.

 THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE
 SUBSTANCE IDENTIFICATION.

=> s vascular endothelial growth factor or vegf

        197586 VASCULAR
         47598 ENDOTHELIAL
        440125 GROWTH
        339460 FACTOR
           822 VASCULAR ENDOTHELIAL GROWTH FACTOR
                 (VASCULAR(W)ENDOTHELIAL(W)GROWTH(W)FACTOR)
           707 VEGF
L1         884 VASCULAR ENDOTHELIAL GROWTH FACTOR OR VEGF

=> s vegf3 or vegf-3

             0 VEGF3
           707 VEGF
       1463151 3
             2 VEGF-3
                 (VEGF(W)3)
L2           2 VEGF3 OR VEGF-3

=> d 1-


L2   ANSWER 1 OF 2  MEDLINE
AN   97342551     MEDLINE
TI   Sequencing of the human vascular endothelial growth factor (
     VEGF) 3' untranslated region (UTR): conservation
     of five hypoxia-inducible RNA-protein binding sites.
AU   Levy N S; Goldberg M A; Levy A P
CS   Department of Medicine, Georgetown University Medical Center,
     Washington, DC 20007, USA.
NC   1F32HL08838-03 (NHLBI)
```

DK45098 (NIDDK)
1KO8HL03405-01 (NHLBI)
SO BIOCHIMICA ET BIOPHYSICA ACTA, (1997 May 30) 1352 (2) 167-73.
Journal code: A0W. ISSN: 0006-3002.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-Y08736; GENBANK-J03145
EM 9709
EW 19970903

L2 ANSWER 2 OF 2 MEDLINE
AN 96162020 MEDLINE
TI Post-transcriptional regulation of vascular endothelial growth factor by hypoxia.
AU Levy A P; Levy N S; Goldberg M A
CS Cardiology Division, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.
NC T32HL07604 (NHLBI)
IKO8HL03405-01 (NHLBI)
1F32HL08838-02 (NHLBI)
+
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Feb 2) 271 (5) 2746-53.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-U22372; GENBANK-M10244
EM 9605

=> s vegf-b

707 VEGF
356450 B
L3 6 VEGF-B
(VEGF(W)B)

=> d 1-

L3 ANSWER 1 OF 6 MEDLINE
AN 97332628 MEDLINE
TI Comparison of VEGF, **VEGF-B**, VEGF-C and Ang-1 mRNA regulation by serum, growth factors, oncoproteins and hypoxia.
AU Enholm B; Paavonen K; Ristimaki A; Kumar V; Gunji Y; Klefstrom J; Kivinen L; Laiho M; Olofsson B; Joukov V; Eriksson U; Alitalo K
CS Molecular/Cancer Biology Laboratory, University of Helsinki, Finland.
SO ONCOGENE, (1997 May 22) 14 (20) 2475-83.
Journal code: ONC. ISSN: 0950-9232.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9709
EW 19970901

L3 ANSWER 2 OF 6 MEDLINE
AN 97167624 MEDLINE
TI Expression of vascular endothelial growth factor and placenta growth factor in human placenta.
AU Vuorela P; Hatva E; Lymboussaki A; Kaipainen A; Joukov V; Persico M G; Alitalo K; Halmesmaki E

CS Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Finland. piia.vuorela@helsinki.fi
SO BIOLOGY OF REPRODUCTION, (1997 Feb) 56 (2) 489-94.
Journal code: A3W. ISSN: 0006-3363.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9706
EW 19970604

L3 ANSWER 3 OF 6 MEDLINE
AN 97164697 MEDLINE
TI VEGF-C receptor binding and pattern of expression with VEGFR-3 suggests a role in lymphatic vascular development.
AU Kukk E; Lymboussaki A; Taira S; Kaipainen A; Jeltsch M; Joukov V; Alitalo K
CS Molecular/Cancer Biology Laboratory, Haartman Institute, University of Helsinki, Finland.
SO DEVELOPMENT, (1996 Dec) 122 (12) 3829-37.
Journal code: ECW. ISSN: 0950-1991.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-X68203; GENBANK-U73620
EM 9705
EW 19970501

L3 ANSWER 4 OF 6 MEDLINE
AN 96325041 MEDLINE
TI Genomic organization of the mouse and human genes for vascular endothelial growth factor B (**VEGF-B**) and characterization of a second splice isoform.
AU Olofsson B; Pajusola K; von Euler G; Chilov D; Alitalo K; Eriksson U
CS Ludwig Institute for Cancer Research, Stockholm Branch, Box 240, S-171 77 Stockholm, Sweden.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Aug 9) 271 (32) 19310-7.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
OS GENBANK-U52819; GENBANK-U52820
EM 9611

L3 ANSWER 5 OF 6 MEDLINE
AN 96220114 MEDLINE
TI Novel human vascular endothelial growth factor genes **VEGF-B** and VEGF-C localize to chromosomes 11q13 and 4q34, respectively.
AU Paavonen K; Horelli-Kuitunen N; Chilov D; Kukk E; Pennanen S; Kallioniemi O P; Pajusola K; Olofsson B; Eriksson U; Joukov V; Palotie A; Alitalo K
CS Molecular/Cancer Biology Laboratory, Haartman Institute, Helsinki, Finland.
SO CIRCULATION, (1996 Mar 15) 93 (6) 1079-82.
Journal code: DAW. ISSN: 0009-7322.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
OS GENBANK-U48800; GENBANK-X94216
EM 9610

L3 ANSWER 6 OF 6 MEDLINE
AN 96197355 MEDLINE
TI Vascular endothelial growth factor B, a novel growth factor for endothelial cells.
AU Olofsson B; Pajusola K; Kaipainen A; von Euler G; Joukov V; Saksela O; Orpana A; Pettersson R F; Alitalo K; Eriksson U
CS Ludwig Institute for Cancer Research, Stockholm, Sweden.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Mar 19) 93 (6) 2576-81.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
OS GENBANK-U48800; GENBANK-U48801
EM 9609

=> d 1- abs

L3 ANSWER 1 OF 6 MEDLINE
AB The vascular endothelial growth factor (VEGF) family has recently been expanded by the isolation of two additional growth factors, **VEGF-B** and VEGF-C. Here we compare the regulation of steady-state levels of VEGF, **VEGF-B** and VEGF-C mRNAs in cultured cells by a variety of stimuli implicated in angiogenesis and endothelial cell physiology. Hypoxia, Ras oncoprotein and mutant p53 tumor suppressor, which are potent inducers of VEGF mRNA did not increase **VEGF-B** or VEGF-C mRNA levels. Serum and its component growth factors, platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) as well as transforming growth factor-beta (TGF-beta) and the tumor promoter phorbol myristate 12,13-acetate (PMA) stimulated VEGF-C, but not **VEGF-B** mRNA expression. Interestingly, these growth factors and hypoxia simultaneously downregulated the mRNA of another endothelial cell specific ligand, angiopoietin-1. Serum induction of VEGF-C mRNA occurred independently of protein synthesis; with an increase of the mRNA half-life from 3.5 h to 5.5-6 h, whereas **VEGF-B** mRNA was very stable (T 1/2>8 h). Our results reveal that the three VEGF genes are regulated in a strikingly different manner, suggesting that they serve distinct, although perhaps overlapping functions in vivo.

L3 ANSWER 2 OF 6 MEDLINE
AB Normal development and function of the placenta requires invasion of the maternal decidua by trophoblasts, followed by abundant and organized vascular growth. Little is known of the significance and function of the vascular endothelial growth factor (VEGF) family, which includes VEGF, **VEGF-B**, and VEGF-C, and of placenta growth factor (PIGF) in these processes. In this study we have analyzed the expression of VEGF and PIGF mRNAs and their protein products in placental tissue obtained from noncomplicated pregnancies. Expression of VEGF and PIGF mRNA was observed by in situ hybridization in the chorionic mesenchyme and villous trophoblasts, respectively. Immunostaining localized the VEGF and PIGF proteins in the vascular endothelium, which was defined by staining for von Willebrand factor and for the Tie receptor tyrosine kinase, an early endothelial cell marker. **VEGF-B** and VEGF-C mRNAs were strongly expressed in human placenta as evidenced by Northern blot analysis. These data imply that VEGF and PIGF are produced by different cells but that both target the endothelial cells of normal human term placenta.

L3 ANSWER 3 OF 6 MEDLINE

AB The vascular endothelial growth factor family has recently been expanded by the isolation of two new VEGF-related factors, **VEGF-B** and VEGF-C. The physiological functions of these factors are largely unknown. Here we report the cloning and characterization of mouse VEGF-C, which is produced as a disulfide-linked dimer of 415 amino acid residue polypeptides, sharing an 85% identity with the human VEGF-C amino acid sequence. The recombinant mouse VEGF-C protein was secreted from transfected cells as VEGFR-3 (Flt4) binding polypeptides of 30-32x10(3) Mr and 22-23x10(3) Mr which preferentially stimulated the autophosphorylation of VEGFR-3 in comparison with VEGFR-2 (KDR). In in situ hybridization, mouse VEGF-C mRNA expression was detected in mesenchymal cells of postimplantation mouse embryos, particularly in the regions where the lymphatic vessels undergo sprouting from embryonic veins, such as the perimetanephric, axillary and jugular regions. In addition, the developing mesenterium, which is rich in lymphatic vessels, showed strong VEGF-C expression. VEGF-C was also highly expressed in adult mouse lung, heart and kidney, where VEGFR-3 was also prominent. The pattern of expression of VEGF-C in relation to its major receptor VEGFR-3 during the sprouting of the lymphatic endothelium in embryos suggests a paracrine mode of action and that one of the functions of VEGF-C may be in the regulation of angiogenesis of the lymphatic vasculature.

L3 ANSWER 4 OF 6 MEDLINE

AB A second isoform and the genomic structures of mouse and human vascular endothelial growth factor B are described. Both genes consist of seven coding exons and span about 4 kilobases of DNA. The two identified isoforms of vascular endothelial growth factor B are generated by alternative splicing where different splice acceptor sites in exon 6 introduce a frameshift and a partial use of different but overlapping reading frames. Consequently, the COOH-terminal domains in the two isoforms show no resemblance. Mouse and human cDNA clones for the novel isoform of vascular endothelial growth factor B encoded a secreted protein of 186 amino acid residues. Expression in transfected cells generated a protein of 25 kDa which upon secretion was modified by O-linked glycosylation and displayed a molecular mass of 32 kDa under reducing conditions. The protein was expressed as a disulfide-linked homodimer, and heterodimers were generated when coexpressed with vascular endothelial growth factor. The entirely different COOH-terminal domains in the two isoforms of vascular endothelial growth factor B imply that some functional properties of the two proteins are distinct.

L3 ANSWER 5 OF 6 MEDLINE

AB BACKGROUND: Vascular endothelial growth factor (VEGF) is an important regulator of endothelial cell proliferation, migration, and permeability during embryonic vasculogenesis as well as in physiological and pathological angiogenesis. The recently isolated **VEGF-B** and VEGF-C cDNAs encode novel growth factor genes of the VEGF family. METHODS AND RESULTS: Southern blotting and polymerase chain reaction analysis of somatic cell hybrids and fluorescence in situ hybridization (FISH) of metaphase chromosomes were used to assess the chromosomal localization of **VEGF-B** and VEGF-C genes. The **VEGF-B** gene was found on chromosome 11q13, proximal to the cyclin D1 gene, which is amplified in a number of human carcinomas. However, **VEGF-B** was not amplified in several mammary carcinoma cell lines containing amplified cyclin D1. The VEGF-C gene was located on chromosome 4q34, close to the human aspartylglucosaminidase gene previously mapped to 4q34-35. CONCLUSIONS: The **VEGF-B** locus in 11q13 and the VEGF-C locus in 4q34 are candidate targets for mutations that lead to vascular malformations or cardiovascular diseases.

L3 ANSWER 6 OF 6 MEDLINE

AB We have isolated and characterized a novel growth factor for endothelial cells, vascular endothelial growth factor B ( **VEGF-B**), with structural similarities to vascular endothelial growth factor (VEGF) and placenta growth factor. **VEGF-B** was particularly abundant in heart and skeletal muscle and was coexpressed with VEGF in these and other tissues. **VEGF-B** formed cell-surface-associated disulfide-linked homodimers and heterodimerized with VEGF when coexpressed. Conditioned medium from transfected 293EBNA cells expressing **VEGF-B** stimulated DNA synthesis in endothelial cells. Our results suggest that **VEGF-B** has a role in angiogenesis and endothelial cell growth, particularly in muscle.